



## SIGNIFICANCE OF VENTRICULAR REPOLARIZATION ABNORMALITIES IN DENGUE VIRAL FEVER

### General Medicine

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### ABSTRACT

Infection by Dengue virus (DENV) is an arboviral disease affecting large no of population every year especially in underdeveloped and developing countries. In India every year, lacks of people suffer from it and mortality is well known in both DHS & DSS type of manifestations. Vector responsible is a mosquito, *Aedes aegypti* and/or *Aedes albopictus*. It breeds in fresh water bodies. Disease presents as fever with accompanying symptoms like, body ache, headache, nausea, vomiting, hemorrhagic spots or bleedings from various sites. Most common laboratory findings are leucopenia and thrombocytopenia. ECG changes do occur in this disease in relation to myocardial edema, however little importance has been given regarding ventricular repolarization so far. This study has been aimed to evaluate the QTc and QT interval dispersion to recognize ventricular repolarization changes in patients suffering from Dengue viral fever and to assess the grade of severity in relation to prognosis and referring a case to higher center for necessary evaluation and management of dengue fever and its complications. Fifty consecutive patients were included in study during dengue epidemic period. ECG of fifty age and sex matched normal individuals recorded as control group. Routine laboratory tests were performed along with 12 lead ECG. Interval values of QT, QTc and QT dispersion were specially calculated with care in addition to other variables. QTc and QT intervals of both groups were compared for statistical significance and values of case group were found significantly higher (p-value <0.05), for QTc values. No significant difference detected in QT values while QT dispersion found to have weak correlation in this study. This was concluded that ventricular repolarization do suffer in dengue fever, as disease is affecting multiple organs including heart causing temporary myocardial injury and edema. It is worthwhile to record 12 lead ECG in all cases of dengue fever which is otherwise not a routine investigation unless patients develop complications.

### KEYWORDS

Dhs, Dengue Hemorrhagic Syndrome, Dss, Dengue Shock Syndrome, Qtc, Qt Corrected For Heart Rate

### INTRODUCTION

Every year, dengue virus infects about 390 million people in more than hundred countries. About 25% of these progresses to a clinical picture of dengue viral fever.<sup>1</sup> It is caused by 4 different strains of DENV transmitted by vector bite in early morning and early evening time on exposed body parts, mostly limbs.<sup>1,2,3</sup> *Aedes mosquito* breeds in small fresh water collections. After incubation period most common symptoms are fever, headache, retrobulbar pain, body aches and pains, nausea and vomiting. In few cases, right hypochondria pain, anorexia, epigastric pain and shortness of breath<sup>1</sup>. It is easy to diagnose DENV infection by simple routine investigations and with clinical settings of DHS, DSS, and multiorgan failure.

Cardiac involvement is in the form of supra-ventricular or ventricular pre-mature beats, conduction blocks, myocarditis and pericardial effusion<sup>4,5</sup>. Thus, myocardial involvement gives rise to poor chronotropic effect. During epidemics the prevalence of myocarditis reaches up to twelve percent. The abnormalities detected in electrocardiogram due to cardiac dysfunction have been associated with severity and complications in DENV, even before their appearances in clinical settings<sup>6,7</sup>. In routine it is not a practice to record an ECG in uncomplicated case of DENV. So, there are not enough studies available for commenting about myocardial repolarization status in uncomplicated dengue fever cases and even in super review publications on the subject of dengue fever and its complications. Also, there is not much regarding review of ECG changes and an ECG dependent myocardial contractility functions<sup>5</sup>.

The objective of this study was to assess indices of ventricular repolarization during dengue epidemics or otherwise, so that one may predict serious outcomes in case of progression in QT-QTc intervals and alterations in parameter of QT dispersion. It is aimed to suggest peripheral health centers for recording a 12-lead ECG in all cases suffering from DENV. It is important to mention that machines with automatic interpretation will serve the purpose for quick evaluation of lengthened QT-QTc interval and to refer a case to higher center accordingly. QT dispersion calculation is not possible at PHC and CHC level and also this is not a part of ECG machine automatic interpretation.

### METHODOLOGY

There was a DEN outbreak of serotype 1 & 2 in NCR region especially in Gurugram and its surrounding peri-urban and rural areas in 2017 during the month of September to November. Patients visiting SGT

Medical College Hospital, medicine OPD and admitted through emergency in Unit-1 Medicine were registered for this study. Equal no of age and sex matched healthy subjects were also registered for this study and ECG was recorded in all 50 controls for the purpose of comparison of its variables. Several ECG parameters of ventricular repolarization intervals like QT, QTc and QT dispersion were calculated for evaluation of myocardial injury due to DENV.

### INCLUSION CRITERIA

- Both male and female patients
- Age more than 14 yrs of age
- No bar for upper limit
- Terminal cases

### EXCLUSION CRITERIA

- Too sick a patient
- Patients with complications

Patients diagnosed clinically as suffering from DENV, who had (fever plus other two symptoms: severe headache, body aches and pain, retrobulbar pain, muscular pain, joint pain, nausea vomiting, hemorrhagic skin spots) and thrombocytopenia/leucopenia were subjected for ECG recording. NS1 antigen got tested within first four days of symptoms and positive cases included while cases with positive IgM antibody test were also included.

An informed consent was obtained from 50 patients as well as from normal controls. It was approved by Ethical and Research Committee SGT University. The digital 12 lead and three channels ECG machine manufactured by *mindray with automatic interpretation was used for ECG recording. These were HR and intervals of PR, QRS, QT, and QTc. Intervals.*



Fig.1. ECG machine

Bazett's formula,  $QTc = QT\sqrt{R} - R$  (msec)<sup>9,10</sup>.

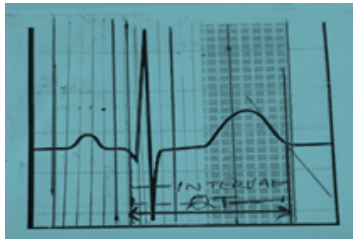


Fig.2. ECG –QT interval

QT interval dispersion is defined as the difference between maximum and the minimum QT interval<sup>10,11</sup>. This calculation is not needed as it needs super specialist to calculate it or QT calculation specialist. Various parameters of the 12 lead ECG of patients groups were compared with age and sex matched controls. Upper limit of QTc interval was considered 450 msec. for women and 470 msec. for men before labeling it a long QTc interval and is predispose to life threatening arrhythmias<sup>12</sup>. Data were tabulated as mean  $\pm$  standard deviation. t-test was used to compare variables between DENV patients and controls. Difference between groups at a p-value <0.05 were considered statistically significant.

**RESULTS & DISCUSSION**

Patients presented on the day of admission with following symptoms, fever in 50(100%), body ache in 44(88%), headache in 46(92%), retrobulbar pain in 38(76%), nausea in 43(86%), anorexia in 32(64%), vomiting in 20(40%), abdominal pain in 18(36%), diarrhea in 12(24%), hemorrhagic spots in 7(14%), bleeding in 2 in 2(4%). mean age was 32.3 $\pm$ 12.0 yrs; and mean systolic blood pressure was 112.9 $\pm$ 14.8, diastolic blood pressure 71.8 $\pm$ 9.29. Mean values found for, Hb was 12.7gm%, TLC 4227/ cmm, and platelets count was detected 0.99 $\pm$ .67L. (Table-1)

**Table 1. VITAL PARAMETERS / LAB INVESTIGATION**

1	Age	32.3 $\pm$ 12.0
2.	Systolic BP	112.9 $\pm$ 14.8
3.	Diastolic BP	71.8 $\pm$ 9.29
4.	Hb%	12.
5.	TLC	5446
6.	Platelet count.	.99 $\pm$ .67L
7.	Total bilirubin	.5 $\pm$ .4
8.	Direct bilirubin	.26
9.	Indirect bilirubin	.32
10.	AST	129.26
11.	ALT	103.9
12.	ALP	112.6
13	SUA	4.89 $\pm$ 1.29
14.	S.CAL	7.86 $\pm$ .76
15.	S.Na+	134.7 $\pm$ 2.6
16.	S. K+	3.8 $\pm$ 0.6

Details of ECG parameters in patient group vs. control group are shown in table no 2. No significant difference detected in various electrocardiographic variables except in QTc interval. QTc interval was prolonged as compared to normal group value and was also highly statistical significant (p-value < 0.001). Only three patients had abnormally long QTc interval while normal group had none. There was no QT dispersion difference between DENV patients and controls. In DENV there is generalized viral invasion in various tissues and a direct tissue injury or by cytokine induced inflammatory process, there is edema of different tissues according to severity of disease or grade of inflammatory response. It can range from tissue edema to fluid collection in the form of peritoneal, pericardial and pleural effusion. In response to this phenomenon, tissue functions suffer, but myocardial repolarization abnormality is reflected in the form of lengthening of QTc interval and abnormalities of QT

**TABLE 2. SYMPTAMATOLOGY**

Fever	50	100%
Headache	46	92%
Body ache	44	88%

Nausea	43	86%
Anorexia	32	64%
Vomiting	20	40%
Abdominal pain	18	36%
Diarrhea	12	24%
Purpuric spots	07	14%
Bleed	02	04%

dispersion much before the full blown picture of myocarditis and myocardial edema and pericardial effusion. A variation in HR and BP could be appreciated on day to day basis. DENV causes a cytokine induced myocardial injury, responsible for ventricular repolarization abnormalities, as observed in this and other studies of past. It is known that dengue viral invasion in the myocardium may lead to a cytokine release, which can result in mild to severe myocardial injury and occasionally turns in fulminating myocarditis<sup>4</sup>.cellular level mechanism behind these findings is still not very clear but it is reasonably explained that myocarditis secondary to DENV might have played a role<sup>13</sup>. There is a study, where DENV myocardial injury lead to a stage of cardiomyopathy, known as Takatsubo Cardiomyopathy and this change stayed for eight days before coming to normality without any specific treatment<sup>14</sup>. As per guidelines for peripheral health care institutions, neither there is provision for 2D-ECHO nor for troponin serum levels needed to diagnose and evaluate myocarditis. Therefore, this study emphasizes the need and importance of 12 Lead ECG, which is an inexpensive, noninvasive, simple and indicative of subtle cardiac disease. Patients with abnormalities in ECG should be subjected to 2D-ECHO and cardiac markers estimation in higher health facilities with intensive care unit.

**Table 3. Case and Control group comparison of various ECG variables.**

Variables	DENV (50)--A	Controls (50)--B	A:B p-value
Sinus tachycardia	2	0	
Sinus bradycardia	2	0	
HR	80.2 $\pm$ 11.3	77.7	NS
PR-interval (msec)	140.0 $\pm$ 11.0	142.5	NS
QRS interval (msec)	88.1 $\pm$ 11.0	83.6 $\pm$	NS
QT interval msec)	373.06 $\pm$ 61.7	362.38 $\pm$ 5	<0.05
Qtc interval (msec)	426.72 $\pm$ 40.30	386.5 $\pm$ 20.8	<0..001
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This study depicts that patients with DENV are found to have significant lengthening of QTc interval but without significant QT dispersion, when both groups' values were compared. Such variations were attributed to myocardial edema<sup>13</sup>. Lengthening of QT/QTc interval in previous studies has been observed in cases with DENV. This change stayed for eight days before coming to normality without specific treatment<sup>14</sup>. In this particular case, the ventricular repolarization activity was associated with appearance of acute cardiomyopathy. Thus, it is evident that there is no primary ventricular repolarization change has been observed in patients with DENV. So, this simple investigation possible at all the primary and secondary care health centers, adds to the knowledge of ventricular repolarization activities in patients suffering from DENV.

QT interval dispersion is a known marker of inhomogeneous myocardial repolarization associated with regional electric abnormalities or patch fibrosis<sup>10,11,13</sup>. No abnormality found in QT dispersion is suggestive of myocardial involvement in DENV is an acute process and is independent of myocardial fibrosis<sup>13</sup>.

Our study has a limitation of small sample size and conducted in view of peripheral primary or secondary health care centers with limited facilities. So, complicated cases of DENV patients were not the part of study and our results cannot be extrapolated to patients with complicated DENV. It is not possible to comment on the post discharge pattern of ECG change reversal due to lack of follow up ECG, in the

present study. Our efforts adds to the medical scientific knowledge regarding this disease by detecting cardio logical alterations in patients without complications of dengue fever and to make appropriate timely referral even while working at Primary Health Centers (PHC)/ community health centers.

## CONCLUSION

In view of our findings of myocardial repolarization changes which have substantial impact on patient's outcome, we do recommend a 12-lead ECG in all patients suffering with DENV at all level health institutions, which is not in investigation protocol till today. As per observations of this study, a 12-lead ECG with automatic interpretation of variables may be provided to each peripheral health centers for recognition of early stage myocardial repolarization and in anticipation of serious manifestation, for purposes of timely referral.

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